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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,863	02/14/2002	Gholam A. Peyman	42561	6337

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,863	PEYMAN, GHOLAM A.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,13-32 and 34-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *28-31* is/are allowed.

6)☒ Claim(s) *1,4-10,13-27,32 and 34-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 CFR 1.114, the Amendment and Applicant's Arguments/Remarks, all filed 05/19/04 is acknowledged.

Claims 1, 4-10, 13-32 and 34-40 are pending. Claims 1, 4, 5, 10, 13-15, 23, 24, 27 and 32 have been amended. New claims 35-40 have been added. Claims 2-3, 11-12 and 33 have been cancelled. Claims 1, 4-10, 13-27, 32 and 34-40 are rejected. Claims 28-31 are allowable.

The scope of the claims is being examined in terms of the presence of two fluorescent dyes that excite at different temperatures in the presence of a bioactive agent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-10, 13-27, 32 and 34-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeimer (US Pat. No. 5,935,942) in view of Khoobehi *et al.* (US Pat. No. 5,976,502) and further in view of Rahman *et al.* (US Pat. No. 3,993,754).

Zeimer teaches methods and materials for chemically treating a target site by utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, wherein the liposomes release their contents of fluorescent dyes at a temperature of approximately 41°C (see reference column 3, line 10 through col. 7, line 64); and abstract.

According to Zeimer, the method involves co-administering intravenously a fluorescent dye encapsulated within heat-sensitive liposomes and a tissue-reactive agent which is effective to cause chemical tissue damage following its activation; non-invasively heating tissue at a pre-determined anatomical locus within the eye so that the heat-sensitive liposomes leak and release their contents into the blood vessel or sinus at the predetermined locus; exciting the fluorescent dye; visually observing a pattern of fluorescent vasculature which develops at the pre-determined locus; and activating the tissue-reactive agent disposed within the blood vessel or sinus so that the blood vessel or sinus is chemically damaged to an extent sufficient to occlude the vessel or sinus (col. 3, lines 10-24).

Zeimer teaches that the blood vessel or sinus is selectively and non-invasively heated to a temperature of approximately 41°C by irradiating with a laser beam having a wavelength absorbed by blood (col. 7, lines 53-57).

The heat-sensitive liposomes include physiologically compatible constituents, such as dipalmitoylphosphatidylcholine and dipalmitoylphosphatidyl-glycerol phospholipids, that permit preparation of liposomes using art-recognized techniques that release their contents at temperatures above those of the mammalian body temperature, i.e., above 37°C. Upon exposure to temperatures at least about 40°C, above mammalian temperature, release occurs by leakage or seepage of the liposomes contents or by lysis of the liposomes (col. 7, lines 10-20).

Additionally, the laser-targeted occlusion method also comprises co-administration of an anti-inflammatory agent or an antibiotic encapsulated within the heat-sensitive liposomes. Antibiotics include anti-bacterial, anti-fungal, anti-neoplastic and anti-parasitic antibiotics. Anti-neoplastic antibiotics include aclacinomycins, bleomycins, chromomycins, mitomycins and the olivomycins (col. 12, lines 51-59).

Zeimer is deficient only in the sense that he does not explicitly teach a first and second encapsulated fluorescent dye.

Khoobehi *et al.* teach a method of observing blood flow through the eye by injecting a carrier, such as liposomes and blood cells containing the dye, into the blood stream whereby the carrier can contain a single dye or a mixture of different dyes. The mixture can be of a first carrier containing a dye capable of fluorescing when exposed to a laser beam in the visible range and a second carrier containing a dye capable of fluorescing when exposed to a red or infrared laser beam. In addition, the cells can be stained with two different lipophilic dyes where the first dye fluoresces when exposed to a red or infrared laser beam and a second dye fluoresces when

exposed to a laser beam in the blue-green spectral range (see reference column 3, line 25 through col. 5, line 5).

It would have been obvious to one of ordinary skill in the art to use either a single fluorescent dye or a mixture of different fluorescent dyes as taught by Khoobehi et al. within the methods taught by Zeimer, because Khoobehi et al. explicitly teach liposomes containing a mixture of dyes which serve to enable the dyes to fluoresce when exposed to various types of lasers (i.e., visible range or infrared-spectral range) and similarly Zeimer teaches a method of chemically treating a target site by utilizing fluorescent dyes in order to visualize patterns of fluorescence. The expected result would be a highly effective method of targeting specific tissue sites and observing carriers, particularly liposomes.

Zeimer does not teach hyperthermally treating tissue for a time sufficient to kill cells.

Rahman *et al.* teach a liposome-encapsulated anti-tumor drug, actinomycin, for cancer chemotherapy wherein the encapsulated drug, actinomycin penetrates into tumor cells where it is slowly released to induce degeneration and death of tumor cells. According to Rahman *et al.*, the liposome-encapsulation of actinomycin is effective in causing degeneration and death of tumor cells, while reducing any toxicity to the host body (see reference column 2, lines 5-38) and Abstract.

It would have been obvious to one of ordinary skill in the art to use the combined teachings of Rahman *et al.* within Zeimer, because Rahman *et al.* teach liposome-encapsulated anti-tumor drugs, such as actinomycin, which is a known antineoplastic agent used to effectively

combat tumor cells and similarly, Zeimer teaches treating target sites by utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, to cause chemical tissue damage. The expected result would be an improved method of employing liposome-encapsulated drugs containing fluorescent dyes to effectively destroy cells, while simultaneously reducing the level of toxicity to the host.

In summary, the primary reference (Zeimer) teaches the use of fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, whereby the dyes are heated to release their contents at a pre-determined anatomical locus. The secondary reference (Khoobehi *et al.*) teaches that it is known to use a mixture of fluorescent dyes using various types of lasers. The tertiary reference (Rahman *et al.*) teaches liposome-encapsulated anti-cancer drugs (i.e., actinomycin) to degenerate and kill cells. It is the position of the Examiner that there is no criticality observed in the instantly claimed temperature of about 45° to about 60° since the claims merely require that the tissues be heated for a sufficient time to kill cells. The tertiary reference of Rahman *et al.* is cited to show that it is well-known to use liposome-encapsulated drugs as a means of chemotherapy for the degeneration and killing of tumor cells. It is *prima facie* obvious to use liposome-encapsulated drugs as a means of treatment in combination with the formulations of the primary references, which provide temperature-indicating means. No criticality is seen in the instantly claimed temperature of about 45° to about 60° since the prior art explicitly teaches effective methods for killing (cancerous) cells.

Response to Arguments

Applicant's arguments filed 05/19/04 have been fully considered but they are not persuasive.

Applicant argued, "Zeimer provides no motivation or incentive to heat the tissue to 45°C as now claimed. The art of record clearly avoids cell and tissue damage, and thus, expressly discloses heating only to about 41°C, which is well known to be the temperature at which little or no tissue and cell damage occurs. The prior Office Action states that Zeimer heats to cause tissue damage. However, this contention is inconsistent with the Zeimer patent as a whole. The passage only recognizes that tissue damage can occur by heat, but provides no suggestion that the Zeimer process intends to or in fact does cause tissue damage by heating."

These arguments have been thoroughly considered but were not found to be persuasive. The primary reference of Zeimer teaches utilizing fluorescent dyes and tissue-reactive substances that are encapsulated within heat-sensitive liposomes, whereby the dyes are heated to release their contents at a pre-determined location. Although Zeimer teaches heating to only about 41°C, the prior art does recognize using liposome-encapsulated materials, such as fluorescent dyes, using a temperature-indicating means and method to effectively chemically treat tissues. The argument that 'the art of record clearly avoids cell/tissue damage' is not persuasive since Zeimer teaches heating tissue to about 41°C, without causing substantial physiological damage (col. 10, lines 9-13), thus indicating that some tissue damage does occur. As delineated above, there is no criticality observed in the instantly claimed temperature of about 45° to about 60° since the claims merely require that the tissues be heated for a sufficient time to kill cells. The tertiary reference of Rahman *et al.* teaches using liposome-encapsulated anti-tumor drugs as a means of

chemotherapy for the degeneration and killing of tumor cells. Hence, in view of the teachings of the prior art of record, the instant invention is rendered *prima facie* obvious.

Allowable Subject Matter

Claims 28-31 are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays from 8:00 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

H. N. Sheikh H.N.S.
Patent Examiner
Art Unit 1615
August 23, 2004

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